Current Fish Vaccine Regulations and Policies: What is and isn't working for fish culturists

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Aquatic Life Sciences

WESTERN CHEMICAL INC.
Product Purity & Environmental Stewardship

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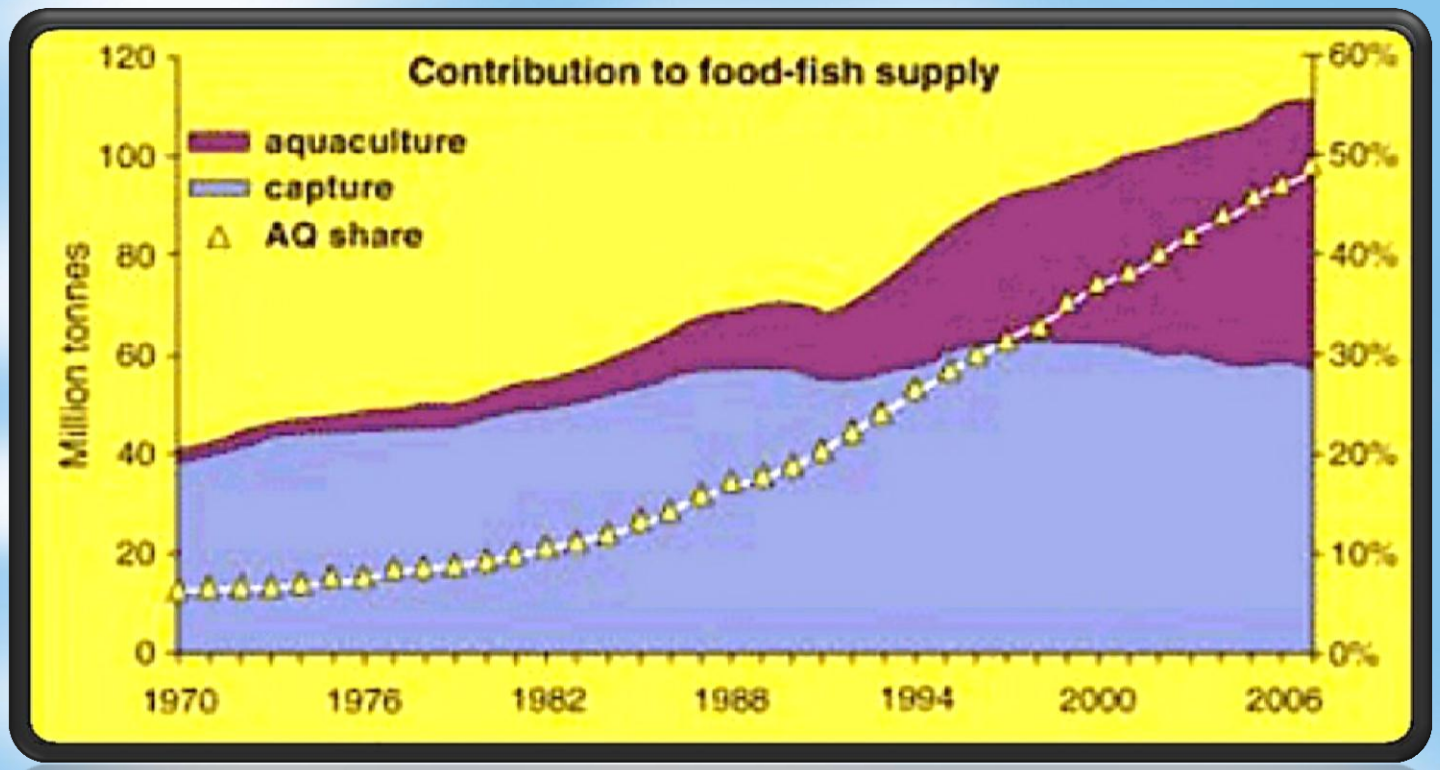
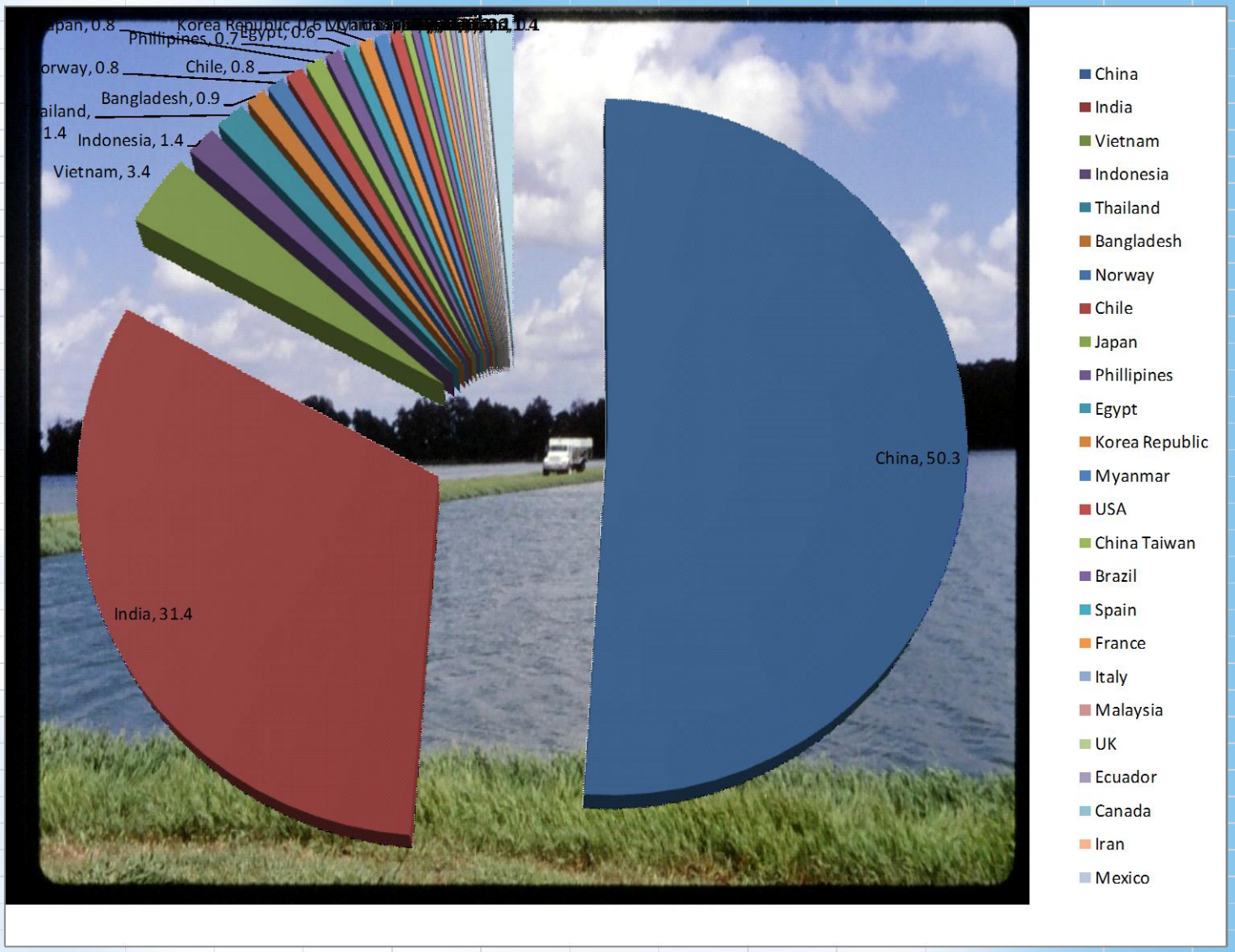

Contribution to food-fish supply
aquaculture
capture
AQ share
Million tonnes
120
100
80
60
40
20
0
60%
50%
40%
30%
20%
10%
0%
1970
1976
1982
1988
1994
2000
2006

US is 14th

GLOBAL AQUACULTURE PRODUCTION IN TONS

	2007 TONS (millions)
China	50.3
India	31.4
Vietnam	3.4
Indonesia	1.4
Thailand	1.4
Bangladesh	0.9
Norway	0.8
Chile	0.8
Japan	0.8
Phillipines	0.7
Egypt	0.6
Korea Republic	0.6
Myanmar	0.6
USA	0.5
China Taiwan	0.3
Brazil	0.3
Spain	0.3
France	0.2
Italy	0.2
Malaysia	0.2
UK	0.2
Ecuador	0.2
Canada	0.2
Iran	0.2
Mexico	0.2
Turkey	0.1
Pakistan	0.1
New Zealand	0.1
Others	1.4



United States Department of Agriculture
Animal and Plant Health Inspection Service

Program Aid No. 1713

Veterinary Biologics:

Use and Regulation

“Types of Veterinary Biologics

• **Vaccines—**made from viruses, bacteria**,** spores, or other disease-causing agents. The organisms in a vaccine are always living except in certain viral vaccines, where the agent is killed. The living organisms in a vaccine may be modified by culture or natural selection so that they do not cause disease.

• **Bacterins and Bacterin–Toxoids—**inactivated cultures of bacteria or other nonviral organisms. If the product contains an inactivated toxin that is immunogenic, it is called abacterin–toxoid.

• **Bacterial Extracts—**purified preparations that contain selected highly immunogenic portions of organisms.

• **Vaccines with Bacterins or Bacterin–-Toxoids—**combinations of biological productsthat may be found in a single container or may be sold in separate containers within the same package.

• **Toxoids—**similar to bacterin-toxoids except that they have been purified to remove bacterial cells.

• **Antiserums and Antitoxins—**products containing antibodies, usually from specifically immunized animals. If the antibody neutralizes a specific toxin, it is called an antitoxin.”

• Also: **Allergenic extracts; Diagnostics; and Miscellaneous immune stimulants**

"Under the 1913 Virus–Serum–Toxin Act, further amended by the 1985 Food Security Act, the U.S. Department of Agriculture's (USDA) Animal and Plant Health Inspection Service (APHIS) is responsible for ensuring that all veterinary biologics produced in or imported into the United States are pure, safe, potent, and effective. This regulatory activity is accomplished by the Center for Veterinary Biologics (CVB) in Ames, IA."

“APHIS’ Role in Safeguarding Biologics

APHIS inspects licensed and permitted manufacturers to be sure that facilities are adequate andp roperly maintained.

Officials examine production methods and records to assure that they comply with Federal requirements.

Such close supervisionis vital because biologics are produced in live systems that have the potential for change if not properly controlled and maintained. “

"Each production run of a biologic—not just the initial one—must be tested to assure that consistent satisfactory production is being maintained.

APHIS is responsible for assuring that licensees maintain proper quality control of the veterinary biologics they produce and continually develop reference standards and test methods to improve product evaluation. $$$$$

Each serial or batch of veterinary biological products is tested for purity, safety, and potency by the licensee."

“Samples of each serial are also submitted for random quality assurance testing by APHIS.

No licensed biological product may be released until APHIS officials substantiate that all required tests have been satisfactorily concluded.”

Categories of Regulated Vaccines:

- Exempt

-Autogenous

-Experimental

-Conditional

-Fully-licensed

“Biologics Exempt From Federal Licensure ********** **Flexibility**

• Products manufactured by veterinarians that are intended solely for use with their clients’ animals under a veterinarian–client–patient relationship

• Products manufactured by individuals or companies for use only in their own animals

• Products manufactured in States with acceptable veterinary biologics regulatory programs and for sale only in those States

• Products manufactured for export in accordance with the Federal Food, Drug, and Cosmetic Act as amended by the Export Reform Enhancement Act of 1996.Other veterinary biological products used in the United States are licensed or permitted by USDA–APHIS–CVB.”

Steps in the Development of a Typical Basic Vaccine

(Autogenous Steps in "RED")

1. Isolation of microbiological agent associated with disease of concern.
2. Characterization & Cultivation of microbiological agent
3. Infection of lab. animals with confirmation of similar disease signs.
4. Challenge model development.
5. Preliminary "bench top" fermentation experiments. (shake flasks & small fermenters/culture chambers, etc.)
6. Preliminary small-volume downstream processing of culture.
7. Wet lab. vaccination, safety and challenge trials with preliminary vaccines.
8. Modification and refinement of above (possible purification / engineering, etc.).
9. Scale-up of culture and processing to production-feasible volumes.
10. Clinical field trials and safety lab. trials.
11. USDA Regulatory licensing with serial batch production.
12. Market usage, feedback, and formulation refinement.

MAIN ELEMENTS (VARIABLES) OF A VACCINE
"Tricks of the trade" vs. patents
(Keys to differences in efficacy and side effects)

1. Strains and numbers of bacteria and viruses grown
2. Concentrations (relative and absolute of above)
3. Combinations of above (synergistic and antagonistic possibilities)
4. How above are produced
5. How above are killed
6. How above are processed
7. Adjuvant used (type and amount)
8. Emulsifier used
9. Total volume administered

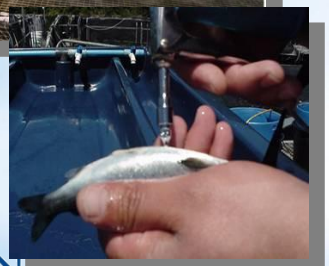
•Each region and even farm has different needs for above

•Best interest of large companies to produce a compromise product for all farms, all regions, etc.

• Large company overhead often inflates COGS **(fish vaccines are THE most inexpensive vaccines/individual of animal vaccines)**

Critical function:
Farm usage, feedback, and formulation refinement.

WORKING WITH AQUACULTURE INDUSTRY TO REFINE FORMULATIONS IS EXTREMELY IMPORTANT!



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Veterinary vaccine prices Jul-11

SPECIES	NAME	Doses	Price	Price per dose	
Sheep & goats	Blue Tongue Type 10	50	13.73	**$0.275**	to veterinarian
Swine	E. coli.	10	7.02	**$0.702**	"
Swine	TrichGuard V5L	50	167.87	**$3.357**	"
Equine	Equimune IV	1	41.33	**$41.330**	"
Cattle and swine	Leptospira	10	4	**$0.400**	"
Swine	Parvo Shield L5E	50	22.47	**$0.449**	"
Swine	Pneumabort-K+1b	10	116	**$11.600**	"
Swine	Rhinomune	1	9.14	**$9.140**	"
Sheep	Camplylobacter	50	25.64	**$0.513**	"
Cattle	Salmonellla	10	4.88	**$0.488**	"
Sheep	Chlamydia	50	45.96	**$0.919**	"
Cattle	Rhinotracheitis-PI3	10	5.41	**$0.541**	"
			Average	**$5.810**	
Poultry	Mareks	5000	14.95	**$0.003**	retail
	Newcastle	5000	12.95	**$0.003**	"
	Infectious bronchitis &ND	1000	4.99	**$0.005**	"
	Fowl pox	1000	6.95	**$0.007**	"
	Hemophilus paragallinarum	1000	36.49	**$0.036**	"
	Mycoplasm gallisepticum	1000	89.95	**$0.090**	"
			Average	**$0.024**	"
Quail and game birds	Quali pox	500	69.97	**$0.140**	

Based on the USDA survey:

49,716 farms produced poultry or eggs valued at $14.5 billion in 1995

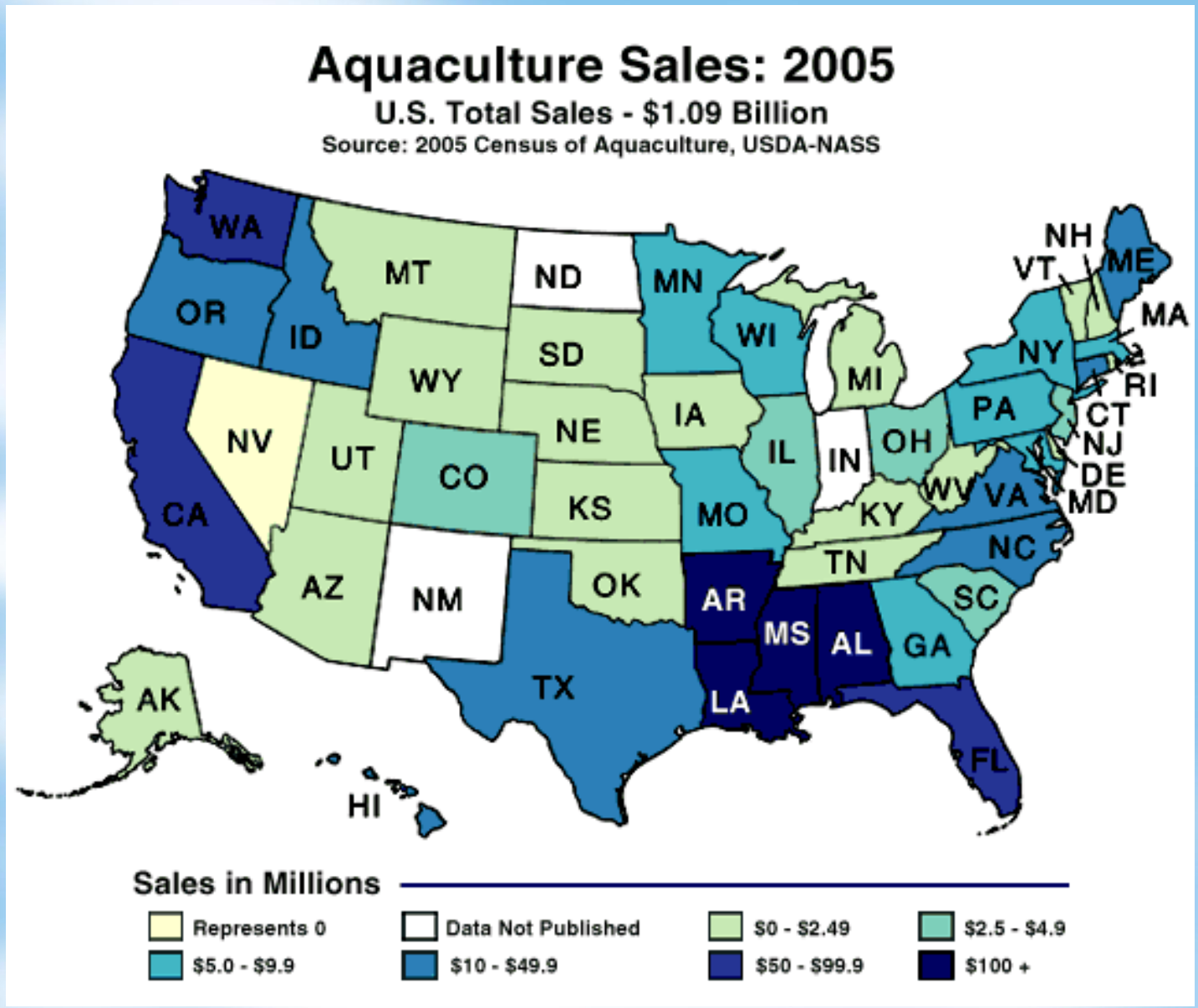
9.08 billion chickens slaughtered in 2008 (USDA)

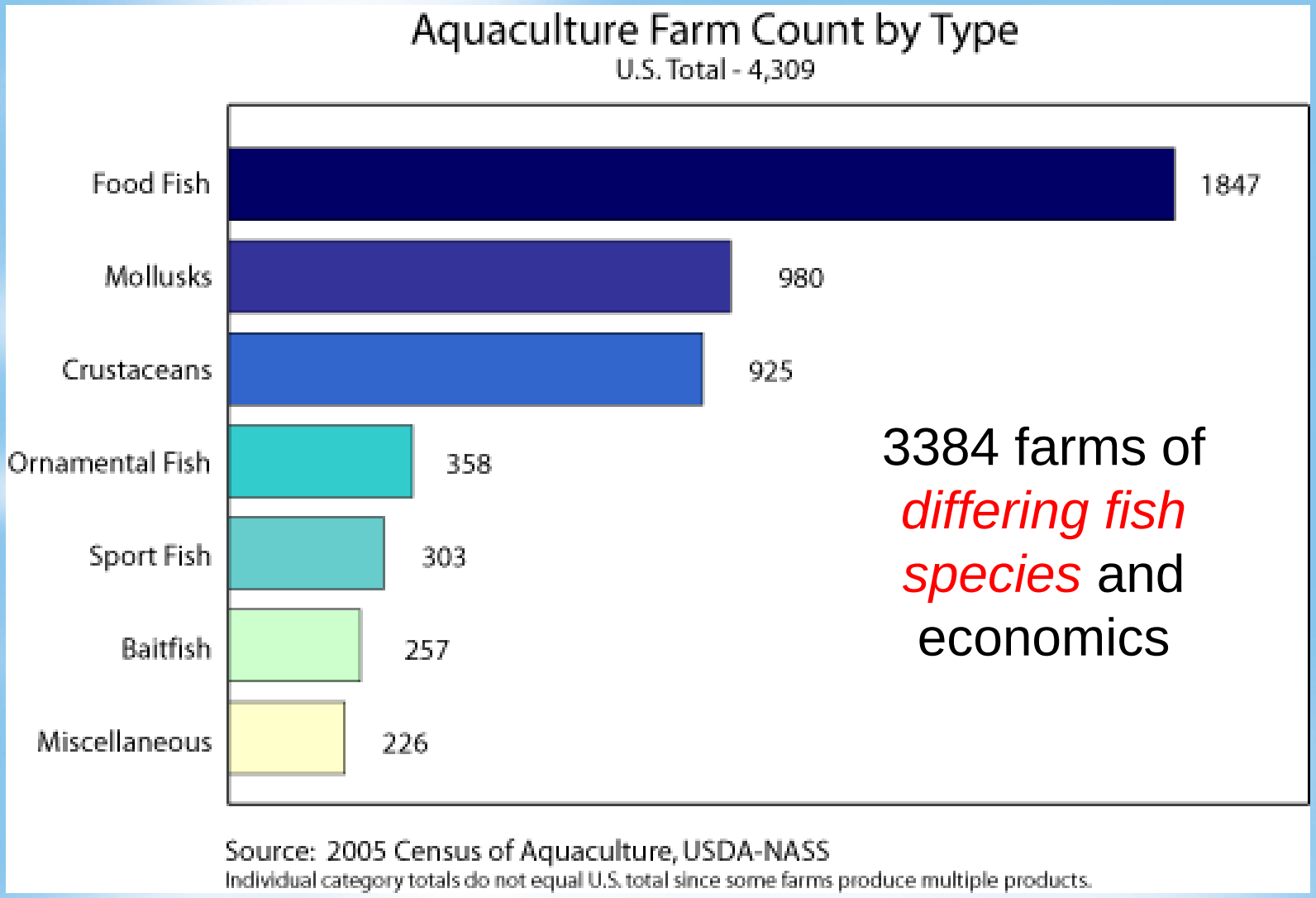
= $235 million retail sales (assume 2.4 cents/dose & 100% vacc.)

US Aquaculture: "Current" status

(2005 Census of Aquaculture, U.S. Department of Agriculture (USDA), National Agricultural Statistics Service (NASS))

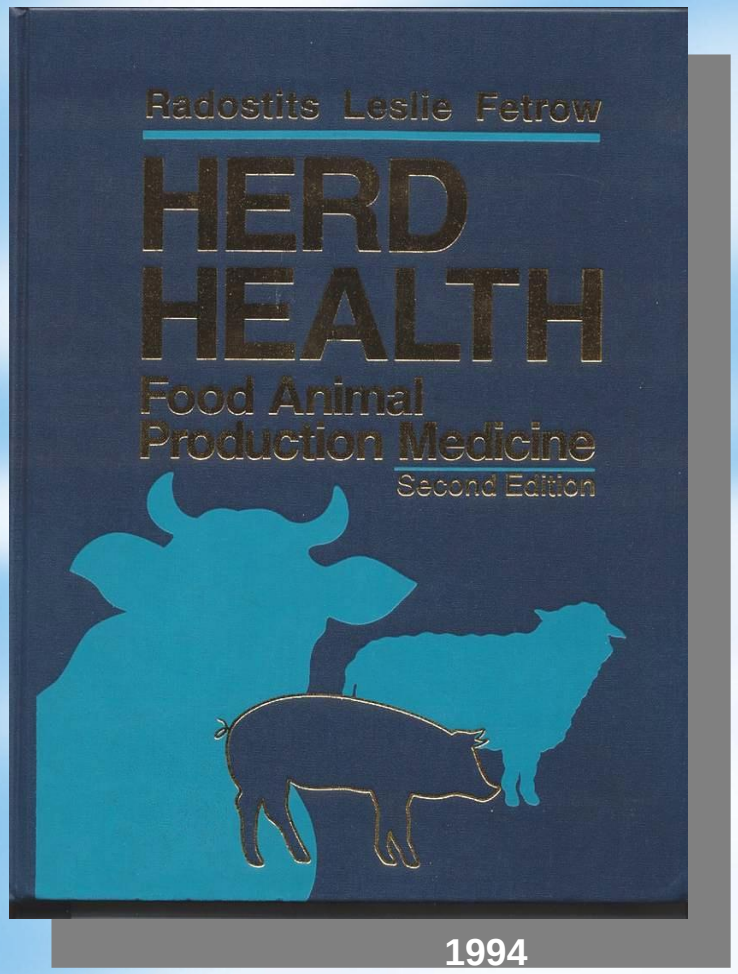
- $1.092 billion dollars of product
- 4309 farms
- Fastest growing segment of U.S. agriculture


Aquaculture Sales: 2005
U.S. Total Sales - $1.09 Billion
Source: 2005 Census of Aquaculture, USDA-NASS
WA
OR
CA
ID
NV
MT
WY
UT
AZ
CO
NM
ND
SD
NE
KS
OK
TX
MN
IA
MO
AR
LA
WI
IL
MS
MI
IN
KY
TN
AL
OH
WV
GA
FL
SC
NC
VA
PA
NY
MD
DE
NJ
CT
RI
MA
VT
NH
ME
AK
HI
Sales in Millions
Represents 0
Data Not Published
$0 - $2.49
$2.5 - $4.9
$5.0 - $9.9
$10 - $49.9
$50 - $99.9
$100 +


Aquaculture Farm Count by Type
U.S. Total - 4,309
Food Fish
1847
Mollusks
980
Crustaceans
925
Ornamental Fish
358
Sport Fish
303
Baitfish
257
Miscellaneous
226
3384 farms of differing fish species and economics
Source: 2005 Census of Aquaculture, USDA-NASS
Individual category totals do not equal U.S. total since some farms produce multiple products.

Fish US Market Vaccine Value	"Guestimation"	Blue Sky	
Species group	**Doses**	**Avg. Price**	**Total value**
Farmed salmon	5000000	$0.070	**$350,000**
Catfish	500000000	$0.005	**$2,500,000**
Trout	54000000	$0.005	**$270,000**
Federal	167000000	$0.001	**$167,000**
Stock enhancement	2000000000	$0.001	**$2,000,000**
Ornamentals	20000000	$0.001	**$20,000**
Baitfish	100000000	$0.001	**$100,000**
Other	10000000	0.025	**$250,000**
		TOTAL	**$5,657,000**

Market uncertainty affects economics/acceptance



"The veterinary practitioner is often asked for advice about the use of vaccines for the control of infectious diseases of food producing animals.

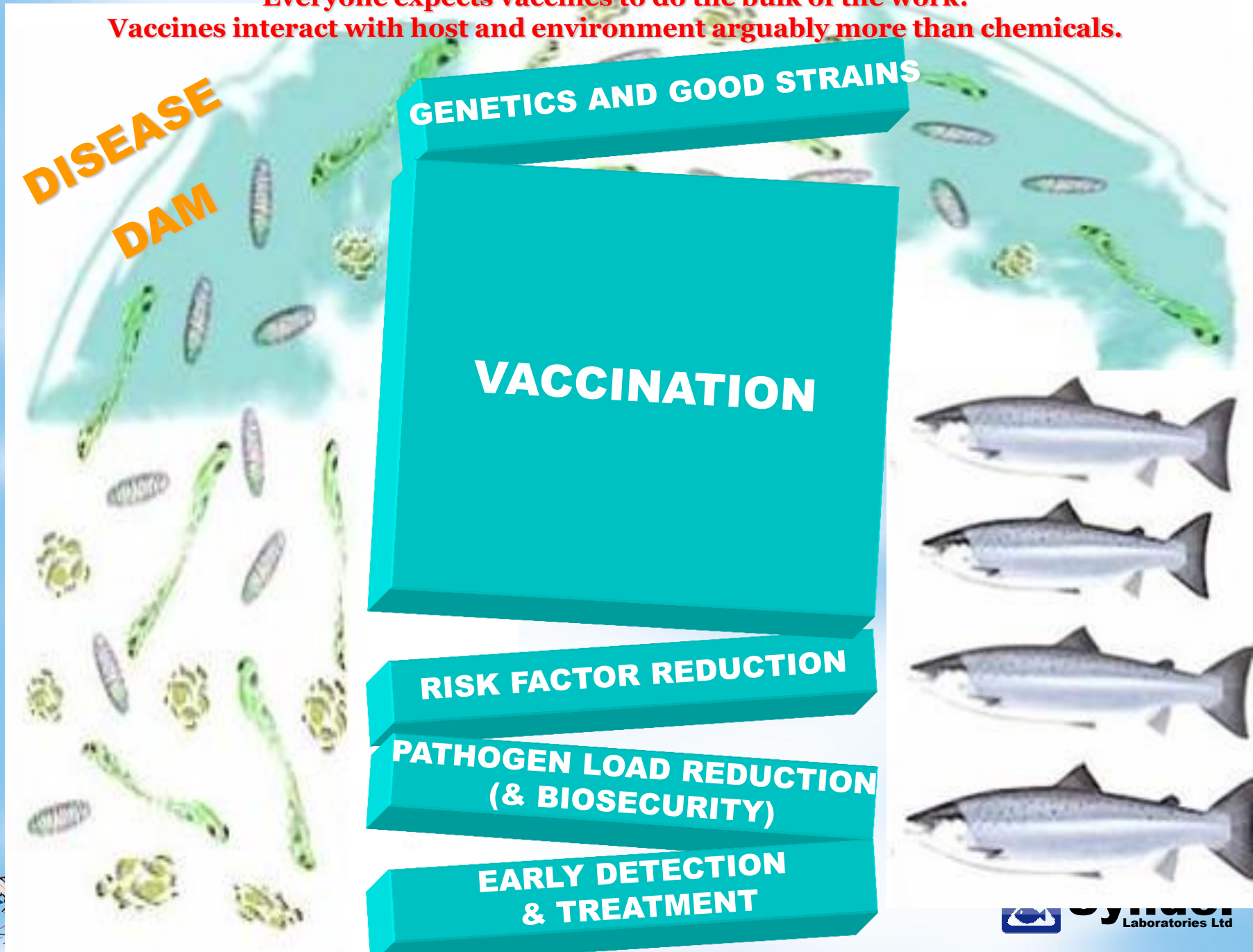
There is often more controversy and uncertainty about the efficacy of these vaccines than about almost any other topic in livestock production".

NOT JUST WITH FISH VACCINES.

"…when veterinarians recommend use of vaccine, the unspoken, implied expectation is that the product will end disease losses. Avoidance of this misunderstanding requires precise and accurate communication of reasonable expectations."

McVey, 1994, ibid...

Everyone expects vaccines to do the bulk of the work!
Vaccines interact with host and environment arguably more than chemicals.



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Ponder:

Does the effect of the environment and fish strain impart more variability on vaccine action than vaccine itself?

Affects:

- **Understanding of nature of vaccines (they are NOT a chemical substitute)**

– **Market acceptability and development initiatives**

– **Investment in market support (overhead)**

What USDA does better than most respective international agencies in fostering and regulating vaccines:

•Recognizes inherent safety (low risk) of vaccines to animals and consumers (vs. perception of pharmaceuticals)

•Accommodating to smaller entities and gives flexibility in Quality Control of manufacturing

•Recognized that “safety” is more important than efficacy (allow “buyer beware” and created expedited and flexible classifications for vaccine development and use (tiered).

•Shows a degree of patience and understanding of the economics and nature of vaccine efficacy and host and environmental interaction (the fuzziness..)

5 Critical Needs for Fish Vaccines from USDA

RECOGNIZE THAT THE ECONOMICS ARE CHALLENGING VS. OTHER SPECIES GROUPS

1. **"MUMS-like" designation for veterinary vaccines based on animal numbers and value (allow even more flexibility in development and manufacture)**

2. **Allow overlap in Function between Autogenous and Conditional and Fully Licensed Production (eliminate requirement for separation for fish facilities)**

3. **Allow for stock regional isolates to be used in autogenous production when none are available (licensed products or autogenous strains)**

4. **Recognize that a vaccine can forever be in transition (a process, not necessarily a product) and, by their nature, can be in continual transition ESPECIALLY for pioneering animal husbandry industries) – facilitate easy "plug-ins" and "–outs" to a basic formula.**

5. **Recognition that genetically altered attentuated strains are just as safe (safer?) than mutagen media created (eg: rifampicin) strains**


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